IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: Application of

Harrington J. *et al.* Art Unit: 1632

Application No.: 09/484,331 Examiner: R. Shukla

Filed: January 18, 2000 Atty. Docket: 0221-0003L

For: Compositions and Methods
For Non-Targeted Activation
of Endogenous Genes

DECLARATION UNDER C.F.R. § 1.132

Assistant Commissioner of
Patents and Trademark
Washington, D.C. 20231

Sir:

The undersigned, Youssef L. Bennani, declares and states:

1. I am Director of Medicinal Chemistry at Athersys, Inc., the subject of the attached Curriculum Vitae and author of the publications shown on the list attached thereto. I was trained as an organic chemist from 1980-1991 (PhD) and have practiced in the field of medicinal chemistry and drug discovery for the past 12 years. I have been part of and led several drug discovery programs in various therapeutic areas at some of the top biopharmaceutical and pharmaceutical companies in the world, including Ligand Pharmaceuticals and Abbott Laboratories. To date, I have been associated with and responsible for discovering 5 or more drugs, one of which is a marketed drug, while others are in various pre-clinical and clinical stages of development. On the basis of

information and facts contained in the above documents and on the basis of my professional history discussed above, I submit that I am an expert in the field of drug discovery and am qualified to speak on the skill and knowledge of the person of ordinary skill in this field.

2. I have read and understand the subject matter of the above-captioned application. I have read and understand the Office Action dated October 25, 2001, rejecting claims 62-68. It is my opinion, based on the scientific evidence and reasons set forth below and in view of my professional experience, that the methods that are the subject of the rejected claims were fully supported by the specification of the above-captioned application and could have been made and used by the person of ordinary skill in the art, as claimed, as of the filing date of September 26, 1997 (Applicants' earliest effective priority date) by routine and ordinary experimentation, using the Applicants' specification as a guide.

Written Description

3. On the issue of written description, it is my understanding that the Examiner has rejected the claims because he believes that the structure of the compound in the claims is critical to practicing the claimed methods and because the specification does not disclose the structures for compounds to be tested, i.e., that there is no "written description" for the compounds.

As I discussed with the Examiner in the interview held on April 17, 2002, the structure of compounds to be tested for activity in the drug discovery process (such as the process claimed) is not critical. Claims 62-68 contain information that can be viewed as an integral part of the drug discovery process. Drug discovery can begin with a cellular system, such as the one described in the above-mentioned claims (62-68), against which random compound libraries are screened for biological activity. It is typical and routine for such screening efforts to encompass large numbers of compounds (in the ten-hundred thousands or millions) in order to maximize hit rates. It is extremely difficult and highly discouraged to pre-select for compounds in such cell-based assays. Therefore, at this stage of the drug discovery process*, compound structure is not a consideration.

*A brief description of the drug discovery process:

A) A gene is linked to a disease state by biochemical, molecular or physiological methods.

B) An in-vitro biochemical or cellular assay (functional or phenotypic) in which such a gene is activated is established.

C) The protein or the cellular system/assay is treated with a compound library containing hundreds to millions of chemical entities (small molecules, peptides, natural products, natural proteins etc.) of wide structural diversity.

D) The ability of any of these chemical entities to perturb (activate or inhibit the protein of interest) in such an assay is determined by physical-chemical methods.

E) The identity of such chemical entities or hits is determined.

F) Such hits are further evaluated for their ability to provide benefit in an in-vivo model of disease and further improved upon based on the resulting data.

G) Additional chemical modification results/should result in chemical entities with acceptable drug parameters (target selectivity, oral bio-availability, efficacy and safety).

H) Such a chemical entity is advanced into human clinical trials.

Enablement

4. On page 7 of the Office Action, the Examiner states that the person of ordinary skill in the art could not determine whether a compound that was isolated by the claimed screening method would have any of the properties of a drug. It is not clear to me why the Examiner believes this. I do not agree with this because such chemical entity, once isolated, constitutes a conventional focal point of the drug discovery process. Such a compound typically contains physical-chemical drug features that may or may not need to be further ameliorated in order to meet all the drug criteria (target selectivity, oral bio-availability, efficacy, good therapeutic index, manufacturing feasibility etc.). It is typical and routine to perform these determinations. Drawing from personal experience I have been involved in several projects that started with a high throughput-screening

program. This allowed the identification of hits, some of which had good drug-like properties that were further modified to become chemical entities with profiles acceptable for clinical drug development. A large majority of drugs, in clinical practice today, have been discovered following a path similar to the drug discovery path described above. This is common practice in our industry.

5. In the paragraph spanning pages 7 and 8 of the Office Action the Examiner states that the person of ordinary skill in the art would not know how to use the claimed method because the specification only discloses that the RAGE-activated cells can be used for drug discovery and that "drug discovery" alone would not convey the specific steps in the claims, particularly steps d and e of claim 62 and step d of claim 63. From this position the Examiner then concludes that the person of ordinary skill in the art would not be able to practice the claimed methods. I do not agree.

In my experience and opinion, the person of ordinary skill in the art (i.e., drug discovery) would immediately recognize the claimed method in the term "drug discovery" and would know how to use the RAGE-activated cells for drug discovery, including the well-known and fundamental steps used in such research field. As mentioned above, a cell-based assay is an integral part of the drug discovery process known to the person of ordinary skill in the art. This assay would be known to necessarily include the steps of treating the cell with a test compound (step C above) and

determining the effect of the test compound on the target (step D above). Therefore, it is my opinion that the artisan would know how to use the RAGE-activated cells for all the steps in the claimed process.

6. In summary, I base my opinions and conclusions on the following:

a. RAGE-activated cells expressing a protein or other phenotype of interest can constitute the first step in the drug discovery process.

b. Cell-based assays are routinely used to randomly screen for compounds, off the shelf, from compound collection libraries, or combinatorial libraries with biochemical or biological activities.

c. Once such compounds are discovered, further chemical modification helps address the various criteria that make up a drug such as: good solubility, good absorption, good tissue distribution, good bio-availability, selectivity and efficacy in the disease of interest as well as good and acceptable safety index.

d. The term "drug discovery" conveys the steps of treating a cell with a compound and determining the effect of the compound

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4/24/02
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Objective: An executive leadership position in the management of a drug discovery team.

Professional Experience

2001-Present ***Director of Medicinal Chemistry***
Athersys Inc., Cleveland, Ohio

1998-2001 ***Senior Group Leader***
Neurological Diseases Research; Global Pharmaceutical R&D-Abbott Laboratories.

- Directed the efforts of 2 chemistry groups (25 Ph.D. & MS/BS level chemists)
- Co-inventor: **ABT-239** (ADHD, psychiatric disorders & obesity) in human Phase I
- Inventor: **ABT-086** (epilepsy/bipolar/migraine disorders) in late pre-clinical phase
- Filed 17 patent applications (large array of chemical platforms/indications)
- Functions included heading chemistry; scientific and managerial cross-functional interactions with process chemistry, pharmacology, biology, ADMET groups
- Scientific-Project presentations to senior scientific and management teams

1997-1998 Infectious Diseases Research; Global Pharmaceutical R&D-Abbott Laboratories.

- Directed the efforts of 3 Group Leaders with 24 Ph.D. & MS/BS level chemists
- Research on novel anti-fungal cyclic lipopeptides: one out-license candidate
- Research on yeast-specific translation factors-Ribogene-collaboration
- Research on Non-immune-suppressive antifungal rapamycin analogues
- Research on anti-GERD agents: **ABT269**, back-up phase II-clinical agent

1996-1997 ***Group Leader***
Metabolic Diseases Research, Global Pharmaceutical R&D-Abbott Laboratories.

- Directed the efforts of 2 Ph.D. and 2 MS level chemists working on growth factors modulation.

1993-1996 ***Research Scientist***
Medicinal Chemistry, Ligand Pharmaceuticals Inc., USA.

- Directly involvement in pre-clinical studies of FDA approved & marketed **LGD1057**: **Panretin®** & **LGD1550 (co-inventor)** (Phase I-IIa) for the treatment of APL & other cancers.
- Co-inventor: tricyclic retinoids and novel aza-retinoids as selective RXR modulators.

1991-1993 ***Postdoctoral Research Fellow***
The Scripps Research Institute, La Jolla, CA, USA; K.B. Sharpless (2001-Nobel Laureate)

- Worked to the development, applications and mechanism of the AD-reaction.

Education

1997-2000	***Masters in Business Administration (MBA)-w/distinction*** Lake Forest Graduate School of Management, IL, USA.
1986-1991	***Philosophy Doctorate in Chemistry (Ph.D.)*** University of Montreal, Canada, S. Hanessian Laboratories.
1981-1986	***Bachelor's & Masters in Chemistry (BS/MS)*** University of Montreal, Canada, S. Hanessian Laboratories.

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- Dr. Andre G. Pernet, CEO-Genset SA (Paris) 33-1-55-04-5900; Ex-VP-R&D, Abbott Labs.
- Dr. Mike Williams, Vice Pesident-Drug discovery, Molecumetics: Tel: 425-990-7437
- Dr. Dave W. Robertson; VP-Research-Neurology, Pfizer; Tel: 616-833-1634
- Professor K. Barry Sharpless; The Scripps Research Institute; Tel: 619-784-7505
- Professor Stephen Hanessian; University of Montreal; Tel: 514-343-6738

Addendum

(Youssef L. Bennani Ph.D.)

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Summary

Over the years, Dr. Bennani has contributed to a wide variety of research programs, therapeutic areas and types of biological/chemical drug-class targets with emphasis on drug candidates. He contributed and is associated with:

- one clinically marketed drug (Panretin) (Ligand Pharmaceuticals)
- one clinical agent presently ongoing human clinical trials (ABT-239- Abbott laboratories)
- two late-stage pre-clinical compounds (ABT-086, and other agent)

Dr. Bennani has published several scientific papers and holds a number of patents (*see addendum*). He has gained experience in managing several research groups and chemistry programs and was involved in establishing and managing several industrial and academic research collaborations throughout his career. In addition to his academic scientific training, he holds a MBA with emphasis on International business, Strategy, and Leadership; and has attended several courses related to personnel and science management. His management experience includes presentations at Scientific Advisory Board meetings (Abbott Laboratories) and several internal strategic Therapeutic Area and Project research reviews as well as international venues. He has managed research operations for a variety of group sizes and diverse scientific, personnel and strategic challenges. His scientific and drug discovery experience spans the following areas:

- Organic & medicinal chemistry/Drug discovery: structure based drug design; natural product synthesis; organic synthesis; peptide chemistry; combinatorial and parallel synthesis; radiochemistry; organometallic asymmetric catalysis; small molecule crystallography.
- Oncology, Metabolic, Infectious and Neurological diseases research (*direct involvement*):
- Intracellular/nuclear receptor modulation (RARs/RXRs/PPARs etc.).
- Cell surface growth factor receptors/cytokine mimicking (EPO/G-CSF/TPO).
- Gastrointestinal motility (Erythromycin based motilides, GPCR-motilin receptors).
- Immunoregulation (Glycoside/Glucans-based research: CR3, PLA2, PGE2, FKBP-TOR/FRAP).
- Antifungal therapy (Glucan Synthase inhibition & Yeast translation factors modulation: EF3 etc.).
- Neurological diseases (GPCR-modulation: ADHD, epilepsy, bipolar disorders, obesity and pain).
- Cross-functional experience in microbiology, molecular biology, *in-vitro & in-vivo*-pharmacology, PK-PD, ADME-Toxicity and Cardiovascular safety.

Patentability of Reach-Through Claims

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Exemplary Reach Through Situations

- 1. Small molecule per se claim, where the molecule is defined as binding to target but not yet identified (e.g. "A receptor [X] agonist").
- 2. Method of screening claim: how effectively does this claim protect a small molecule identified in the screen?
- 3. "Functional use" claim: claim is to a method of treating a disease by a compound defined not by its structure but rather by its ability to bind to a target (e.g. "A method of treating disease [Y] by administering a compound which is a receptor [X] agonist."

Major Patentability Issues

- Utility (35 U.S.C. 101)
  - See Utility Examination Guidelines
    - 66 *Fed. Reg.* 1092 (Jan. 5, 2001)
- Written Description (35 U.S.C. 112, 1st para.)
  - See Written Description Examination Guidelines
    - 66 *Fed. Reg.* 1099 (Jan. 5, 2001)
- Enablement (35 U.S.C. 112, 1st para.)
- Novelty (35 U.S.C. 102)
- Nonobviousness (35 U.S.C. 103)

Receptor Claims

- Major Patentability Issue - Utility
  - If applicant shows at least one specific, substantial, and credible utility for the receptor, and other statutory requirements are met, applicant is entitled to a patent on the receptor per se.

Receptor Claims

- Scope of Protection
  - An inventor with a patent to a specific receptor has the right to exclude others from using said receptor in a screening assay for identifying agonists or antagonists that can be used to treat a disease.
    - 35 U.S.C. 271(a): "Except as otherwise provided in this title, whoever without authority makes, uses, offers to sell, or sells any patented invention, within the United States, or imports into the United States any patented invention during the term of the patent therefor, infringes the patent."
  - Selling drugs that could have been developed through use of the receptor itself is not necessarily infringement

Receptor Agonist Claims

- Types of claims at issue:
  - "A receptor [X] agonist."
  - "A method of treating disease [Y] by administering a compound which is a receptor [X] agonist."

Receptor Agonist Claims

- Major Patentability Issue - Written Description
  - Generic claim to "A receptor [X] agonist." unlikely to comply with written description requirement:
    - No description of structure of representative number of claimed compounds
    - No description of chemical or physical characteristics of representative number of claimed compounds or of function of representative number of claimed compounds (other than binding to identified receptor)
    - Analogous to *Regents of the Univ. of Cal. v. Eli Lilly & Co.*, 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997)(description of how to obtain compounds not sufficient without description of what the compounds are)
      - See also *Fiers v. Revel*, 984 F.2d 1164, 25 USPQ2d 1601 (Fed. Cir. 1993); *In re Ruschig*, 379 F.2d 990, 154 USPQ 118 (CCPA 1967)

Receptor Agonist Claims

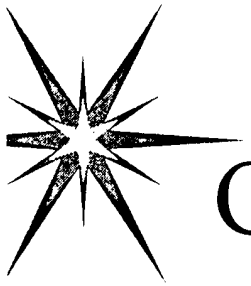
- Major Patentability Issue - Enablement
  - Specification must teach how to make and use the full scope of the claimed invention without undue experimentation.
  - Apply factors set forth in *In re Wands,* 858 F.2d 731,737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)
    - Breadth of the claims
    - Nature of the invention
    - State of the prior art
    - Relative skill of those in the art
    - Level of predictability in the art
    - Amount of direction provided by the inventor(s)
    - Existence of any working examples
    - Quantity of experimentation needed

Receptor Agonist Claims

- Major Patentability Issue - Enablement
  - Generic claim to "A receptor [X] agonist." unlikely to comply with enablement requirement:
    - The specification does not usually teach how to make and use the full scope of agonists or antagonists within that genus without undue experimentation.
    - Specification usually teaches how to identify compounds, rather than how to make them; specification does not usually teach how to use the full scope of the compounds within the genus without undue experimentation.

Receptor Agonist Claims

- Major Patentability Issue - Enablement
  - If a claim to "A receptor [X] agonist" meets the utility, enablement and written description requirements, a claim to "A method of treating disease [Y] by administering a compound which is a receptor [X] agonist" must still be supported by an enabling disclosure.
  - Will compound operate as intended without undue experimentation?



Combinatorial libraries

- Major Patentability Issue - Utility
  - Must have a specific, substantial and credible utility for the collection of elements making up the library (e.g., as an extrinsic research tool)
  - Individual members of the library may not have specific, substantial and credible utilities.
    - *The utility that serves to meet the requirements of 35 U.S.C. §101 relates to the use of the library rather than to the individual members thereof (in the absence of a specific disclosure of a use for an individual member).*

Combinatorial Libraries

- Major Patentability Issue - Written Description
  - A disclosure of a collection of molecules does not necessarily provide support for a claim drawn to any particular individual member of the collection.
  - Possession of a genus does not imply possession of any particular member of genus.
    - *See Fujikawa v. Wattanasin*, 93 F.3d 1559, 39 USPQ2d 1895 (Fed. Cir. 1996) and *In re Ruschig*, 379 F.2d 990, 154 USPQ 118 (CCPA 1967).
    - *See also In re Bell*, 991 F.2d 781, 26 USPQ2d 1529 (Fed. Cir. 1993) and *In re Baird*, 16 F.3d 380, 29 USPQ2d 1550 (Fed. Cir. 1994).

Combinatorial Library

- Scope of protection
  - Right to exclude others from making, using, selling, offering for sale, or importing the library
    - Using a patented library in a screening method for compounds of interest may constitute infringement
  - Does a patented claim to a collection of components confer exclusionary rights to the individual members of the collection?
    - It is the collection of molecules, not the individual components, that is protected by a claim to a combinatorial library.

Methods of Screening (Combinatorial Libraries; Receptors)

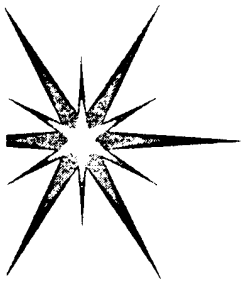
- Major Patentability Issue - Utility
  - Requirement met if screening method identifies a ligand which acts upon a receptor so as to effect a specific, substantial, and credible use
  - Requirement met if the asserted utility for screening a combinatorial library is specific, substantial, and credible.

Methods of Screening (Combinatorial Libraries; Receptors)

- Scope of Protection
  - Claim prevents others from making, using, selling, or offering for sale the claimed screening method.
  - A product identified by a screening method is **not** a product made by a patented process.
    - 35 U.S.C. 271(g) includes use, sale, or importation of a product made by a patented process as an act of infringement.

Products Identified by Methods of Screening (Combinatorial Libraries; Receptors)

- Major Patentability Issues - Written Description and Enablement
  - Same analysis as for receptor agonist claims (discussed earlier)



THANK YOU